Remarks/Arguments

Claims 58-62 are presently in the case.

Priority

Applicants note that the subject matter defined in claims 58- 62 has been accorded an effective filing date of October 16, 2001.

Applicants maintain that the subject matter defined in claims 58-62 is entitled to the priority date of April 1, 1998, Provisional Patent Application Serial No. 60/080328. At page 21, lines 4 - 7 of U.S.S.N. 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family. On page 1, lines 9 - 25, Applicants indicate that neuroligins consitute a multigene family of brain-specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins.

In Serial No. 60/080328, Applicants referenced Ichtchenko et al., *J. Biol. Chem.* 271(5):2676-2682 (1996) and Nguyen and Sudhof, *J. Biol. Chem.* 272(41) 26032-26039 (1997) as references which describe other neuroligins.

Nagase et al., *DNA Research* 6, 337-345 (1999) identifies KIAA 1260 and based on homology identifies this sequence as a neuroligin. KIAA1260 is similar to Applicant's sequence PRO701. This confirms Applicants' statements in Serial No. 60/080328, that PRO701 is a novel neuroligin.

Finally, Applicants enclose a copy of Bolliger et al., *Biochem J.* (2001) 368 581-588 which identified neuroligin 4, which they cloned from human brain based on the sequence of KIAA1260. The polypeptide sequence of neuroligin 4 is similar to PRO701. Bolliger et al., identified that neuroligin 4 binds to PSD-95 which is a characteristic of neuroligins. Finally, Applicants enclose a copy of Jamain et al., *Nature Genetics*, vol. 34, 27- 29 (May 2003) which indicates that mutations of neuroligin 4 are associated with autism. These papers confirm that PRO701 is a neuroligin functioning in mediating recognition processes between neurons.

Based on Applicants disclosure in Serial No. 60/080328, Applicants maintain that they are entitled to priority to the filing date of Serial No. 60/080328, i.e. April 1, 1998. Applicants correctly identified the polypeptide and the utility of the PRO 701 polypeptide. Applicants claimed antibodies to the polypeptide. Later published works by others have simply recognized and confirmed the sequence and utility of the PRO701 polypeptide previously described by Applicants in their priority document.

Specification

Applicants have amended the specification at pages 229 to update the address of the ATCC.

Claim Rejections - 35 U.S.C. § 101 and 112, first paragraph

This application currently stands rejected under 35 U.S.C. § 101 and 112, first paragraph for lack of utility. Applicants disagree with the Examiner for the following reasons.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used

in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Further, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and

direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. 2107.03 (III) states that:

"If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Arguments

First, Applicants rely on the identification of the PRO701 protein as a neuroligin based on homology data. This was first disclosed in U.S. Serial 60/080328 filed April 1, 1998. At page 21, lines 4 - 7 of U.S. Serial 60/080328, Applicants indicate that the PRO701 polypeptide of the invention possesses the biological activity related to that of the neuroligin family. On page 1, lines 9 - 25, Applicants indicate that neuroligins constitute a multi-gene family of brain-specific proteins with distinct isoforms that have overlapping functions in mediating recognition processes between neurons. Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins.

In Serial No. 60/080328, Applicants referenced Ichtchenko et al., *J. Biol. Chem.* 271(5):2676-2682 (1996) and Nguyen and Sudhof, *J. Biol. Chem.* 272(41) 26032-26039 (1997) as references which describe other neuroligins.

Nagase et al., *DNA Research* 6, 337-345 (1999) dentifies KIAA 1260 and based on homology identifies this sequence as a neuroligin. KIAA1260 is similar to Applicant's sequence PRO701. This confirms Applicants' statements in Serial No. 60/080328, that PRO701 is a novel neuroligin with the understood utility of neuroligins.

Finally, Applicants enclose a copy of Bolliger et al., *Biochem J.* (2001) 368 581-588 which further characterized neuroligin 4, which they cloned from human brain based on the sequence of KIAA1260. The polypeptide sequence of neuroligin 4 is similar to PRO701. Bolliger et al., identified that neuroligin 4 binds to the PDZ domains of PSD-95, which is a art recognized characteristic of neuroligins. Finally, Applicants enclose a copy of Jamain et al., *Nature Genetics*, vol. 34, 27- 29 (May 2003) which indicates that mutations of neuroligin 4 are associated with autism.

Based on Applicants disclosure in Serial No. 60/080328 and in the present application, Applicants maintain that the claims are fully enabled. Applicants correctly identified the PRO701 polypeptide as a neuroligin and hence the inherent utility of the PRO701 polypeptide. Later published works by others have simply recognized and confirmed the sequence and inherent utility of the PRO701 polypeptide previously described by Applicants in their priority document.

(2) Second Applicants rely on the "Rat DRG neuronal survival inhibition assay ASSAY #58" for patentable utility for the PRO701 gene and the PRO701 protein and antibodies thereof. This assay first disclosed in PCT/US00/04341 (18 February 2000) and in U.S.S.N. 09/918,585 (30 July 2001) also establishes patentable utility.

The Examiner states that the ability of the PRO701 protein to inhibit the survival of E14 rat embryo dorsal root ganglia is not a credible use because the cells cultured in this assay are not representative of adult neural cells and tumor cells. It is allegedly well known in the art that sensory neurons undergo programmed cell death during early embryonic development. (Oppenheim *Annu. Rev. Neurosci* (1991) Vol. 14, pp 453-501) The art allegedly also teaches that factors that cause neonatal cell death, such as peripheral nerve injury, growth factor withdrawal, ionizing radiation, capsaicin do not have the same effect on adult neural cells. Adult neural cells are allegedly more resistant to these factors (Lewis et al., *J. Neuroscience*, Oct. 1999, Vol. 19(20) pp8945-8953). This is allegedly further exemplified by Memberg et al. who teaches that the survival of neural cells depends on specific factors and that the factor dependence changes with the age of the neural cells. There is allegedly no art-known nexus between the cell

growth of neurons in this assay and the predictable treatment of neuropathies and undesirable neural cell proliferation.

First, Applicants note that the DRG neuronal survival assay is a well recognized and well used assay for measuring compounds which affect the growth of neural cells. The Examiner agrees that the rat DRG neuronal assay has been used in the art to study the effects of various factors on neural development. Applicant note that in vitro sensory ganglia survival and outgrowth assays were used by Levi-Montalcini to identify Nerve Growth Factor. (See excerpt from *Principle of Neural Science* 4th Ed. Kandel ed. (1991) P1056). Secondly Applicants note that both Lewis et al. and Memberg use the DRG survival assay for their analysis. Memberg indicates that proliferation in culture of DRG neuroblasts is consistent with *in vivo* data (page 330, column 1). Clearly this assay is art recognized as being useful to identify compounds with various effects on neural development.

Secondly, in Memberg the comparison was between E12 rat cells and E14.5 rat cells, not between adult and E14.5 rat cells. Memburg indicates that NGF and NT3 act as neurotrophins for E14.5 DRG cells. Memburg does not test whether the neurotrophins which stimulate survival of E14.5 cells are different from those that stimulate survival of adult rat cells. Applicants used E14 rat embryo cells in their assay. This is essentially the same age neurons as Memberg. Memberg does not teach that the use of these neurons is inappropriate.

The Examiner cites Lewis et al. as evidence that adult neural cells are more resistant to peripheral nerve injury. Lewis measured the regulation of HSP27 in DRG of rats by counting the total numbers of HSP27 immunoreactive neurons at postnatal days 2, 7 and 21. Lewis does not measure the regulation of HSP27 in embryonic DRG cells. One of the assays Lewis uses in making his final determination regarding the effect of HSP27 is the DRG survival assay. Lewis determines that the expression of HSP27 confers a survival advantage to neonatal sensory neurons after injury or NGF deprivation. Clearly Lewis, as do others in the field, agree that the DRG neuronal survival assay is a recognized method of assaying for neurotrophic factors.

As set forth in MPEP 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be

imposed. The logic underlying the asserted utility in the present case is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art.

The remaining issue is whether there is sufficient nexus between the *in vitro* data disclosed in the specification and the results a skilled artisan would expect in the treatment of neuropathies. "Nexus" requires a factually and legally sufficient connection between the objective evidence provided and the claimed invention, so that the evidence is of probative value in the determination of the issue that it is purported to support. There are peer-reviewed papers in the literature where the authors have used the DRG survival assay to identify neurotrophins and compounds which inhibit neuronal growth. The Examiner admits that the assay has been used to study the effects of various factors on neural development. Finally, this assay or one similar to it was used in the identification of Nerve Growth Factor which is recognized as being a neurotrophin. Positive results with a drug candidate in a recognized *in vitro* assay have long been recognized by the Patent Office and competent courts as sufficient to support utility for claims covering compounds.

(3) Third, Applicants rely on the "inhibition of MLR assay- ASSAY #67" for patentable utility for the PRO701 gene and the PRO701 protein and antibodies thereof. This assay first disclosed in U.S.S.N. 09/918,585 (30 July 2001) and PCT/US00/04341 (18 February 2000) establishes patentable utility.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit a declaration and supportive references from the art to support the immunoinhibitory activity of PRO701.

Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology and co-inventor of the present application, to show that there are specific immune inhibitory utilities for compounds identified by an MLR assay. The Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. As Dr. Fong emphasizes, immunoinhibitory molecules are important and are very desirable in the treatment of cancer and

in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence for this utility also comes from teachings in the art like Steinman *et al.* (Exhibit B) and Peterson *et al.* (Exhibit D). Steinman *et al.* state that "...**medicine needs therapies that enhance immunity or resistance to infections and tumors.** (page 1, column 1, line 7; emphasis added)". Peterson *et al.* (Exhibit D) show that, recently, the immune stimulant IL-12 was successfully used in a cancer vaccine trial to treat melanoma. Further, as Dr. Fong explains regarding the IL-12 melanoma trial:

> "Due to the immune stimulatory effect of IL-12, **the treatment provided superior results** in comparison to earlier work, where the patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs) treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response" (Emphasis added).

Further, Dr. Fong's declaration clearly states that:

> "It is my considered scientific opinion that a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases. ".

Similarly, as would be readily recognized by one skilled in the art based on the instant specification, the positive results obtained in the MLR assay for PRO701 and the supportive examples in the art, the MLR assay results clearly establish utility for the polypeptides as inhibitors of the immune response. The specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose. Thus, Applicants assert inhibitory uses of PRO701 polypeptides, for example, in the treatment of autoimmune diseases.

Further, since the legal standard accepts *in vitro* assays as acceptable utility and the data is "reasonably correlated" to the pharmacological utility based on the discussions above, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art for the PRO701 polypeptides.

Thus, Applicants believe that they have established patentable utility for PRO701 and its antibodies as instantly claimed and this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 102

1. Claims 58-62 stands rejected under 35 U.S.C. 102(b) as being anticipated by Ichtchenko et al. Ichtchenko et al. allegedly teaches a polypeptide that consists of amino acid residues that correspond to an amino acid epitope of the polypeptide to which the claimed antibody binds.

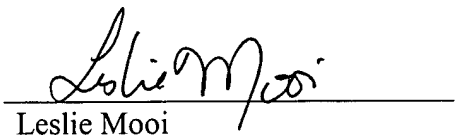
This rejection is respectfully traversed. Applicants respectfully submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Therefore, the term "specifically binds" in Claim 58 (and, as a consequence, those claims dependent from the same) clearly refers to an antibody that is able to bind to the PRO701 polypeptide without significantly cross reacting with another antigen. Applicant is not required to identify the unique epitope in the PRO701 polypeptide. Accordingly, the claims are not anticipated by Ichtchenko et al. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2630P1C20. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 14, 2004



Leslie Mooi
Reg. No. 37,047

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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